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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,256	12/18/2003	James E. Dahlberg	FORS-08497	1902

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EXAMINER	
BABIC, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/740,256	DAHLBERG ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-82* is/are pending in the application.

4a) Of the above claim(s) *35,37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34,36 and 39-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claim(s) 32-82 are pending. Claim(s) 32-34, 36, and 39-82 are under examination. The following Office Action is in response to Applicant's communication dated March 3, 2009.

Claim Rejections - 35 USC § 103 - Withdrawn

Applicant's claim amendments and supplemental remarks are sufficient to overcome the rejection of claim(s) 32,34,35,37-41,48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82 over Ledford, Lane, and Lau.

Claim Rejections - 35 USC § 103 - New Grounds

The following rejection(s) are made in view of applicant's amendment.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim(s) 32, 34, 35, 37-41, 48-54, 57, 60, 61, 63-65, 72-75, 76- 78, 81, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledford et al. ("A multi-site study for detection of the factor V (Leiden) mutation from genomic DNA using a homogeneous invader microtiter plate fluorescence resonance energy transfer (FRET) assay" J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (U.S. 5,770,365), in view of Prudent et al. (U.S. 5,985,557), in view of Rather (U.S. 5,858,367), in view of Rando et al. (U.S. 5,593,835), and in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862).

With regard to claim(s) 32 and 34, it is first submitted that steps a-d of the claimed invention generally encompass an assay, which was known at the time of invention as an Invader Assay (see also Prudent, U.S. 5,985,557), further comprising the use of a probe that when hybridized to the target nucleic acid forms a duplex secondary structure.

Ledford teaches a homogeneous Invader microtitre plate FRET assay (abstract; fig. 1; pg. 100, Invader Assay, for example). Specifically, Ledford teaches a method comprising: a) contacting a target nucleic acids with unlabeled probes forming a detection structure (fig. 1, Invader Oligonucleotide, WT Probe, invasive cleavage structure, for example); b) b) reacting the detection structure with nuclease that cleaves the detection structure (fig.1, released flap; pg. 98-99, col. 1, Cleavase, for example); c) dissociating the target nucleic acid from the unlabeled probes (pg. 99, col. 1, probe turnover, for example); and d) detecting modified detection structure (fig.1, FRET detection of released flap; pg. 98-99, col. 1, FRET, for example).

With regard to claim(s) 39-41, Ledford teaches FRET detection (fig.1, FRET detection of released flap; pg. 98-99, col. 1, FRET, for example).

With regard to claim(s) 48 and 49, Ledford teaches detection of a mutation, i.e. specific type of nucleic acid (abstract; fig. 2, Leiden mutation, for example).

With regard to claim(s) 50, Ledford teaches a cell lysate (pg. 99, col. 2, sample prep., for example).

With regard to claim(s) 52 and 53, Ledford teaches detection of a mutation, i.e. specific type of nucleic acid within a plurality of different nucleic acids (abstract; fig. 2, Leiden mutation, for example).

With regard to claim(s) 32, 60, and 61, refer to the rejection of claim(s) 1 above.

With regard to claim(s) 63-65, refer to the rejection of claim(s) 39-41 above.

With regard to claim(s) 72 and 73, refer to the rejection of claim(s) 48 and 49 above.

With regard to claim(s) 74, refer to the rejection of claim(s) 50 above.

With regard to claim(s) 76 and 77, refer to the rejection of claim(s) 52 and 53 above.

With regard to claim(s) 81 and 82, Ledford teaches two distinct probes (fig. 1, Invader Oligonucleotide, WT Probe, invasive cleavage structure, for example).

With regard to the above claims, Ledford does not expressly teach the use of a probe that when hybridized to the target nucleic acid forms a duplex secondary structure, the formation of a DNA/RNA heteroduplex, or the detection of microRNA fewer than 30 nucleotides.

With regard to the use of probes having secondary structure, Lane provides a supportive disclosure that teaches oligonucleotide probes having a secondary structure wherein the duplex and target regions are within one nucleotide of each other (col. 1-3, summary; col.7, lines 5-25; col. 8, lines 15-30; fig. 1, sections A-D, box 30, for example). Lane expressly teaches that the duplex region of the probe stabilizes, entropically, the target-specific region of the capture moiety and thereby favors formation of a target:probe duplex (col. 7, lines 30-40, for example).

With regard to the formation of a DNA/RNA heteroduplex, it is noted that Ledford teaches the use of DNA to detect a DNA target; however, it is first noted that Prudent (U.S. 5,985,557), part of the original inventive entity of the Invader Assay, expressly envisioned the detection of RNA (col. 10, lines 25-40, for example). Furthermore, it was well known in the art at the time of invention that DNA probes could be used to detect RNA targets. For example, Rather outlines the well known "Northern Blot" assay which

utilizes DNA probes to detect RNA targets (col. 12, lines 50-65, for example). Also, it was well known in the art at the time of invention that DNA was a more stable molecule than RNA (see Rando, U.S. 5,593,835; col. 10, lines 10-20, for example). Thus, it is submitted that one a skill in the art would have found it more practical to select DNA probes over RNA probes for the detection a target sequence due to the instability of RNA.

With regard to the detection of microRNA and claim(s) 51, 54, 75, and 78, Lau provides a supporting disclosure that teaches two types of short RNAs, both about 21 to 25 nucleotides (21-25 nt) in length (lin-4 and let-7) (i.e. microRNA (miRNA)) (abstract; table 1, for example), an obvious structurally equivalent species of the genus molecule RNA. Lau further teaches the detection of miRNAs (fig. 3, for example) as well as the motivation to study these molecules, as their abundance implies that they function in a variety of regulatory pathways.

Thus, in summary, it is submitted that it would have been *prima facie* obvious to one of ordinary skill in that at the time of invention to incorporate probes comprising secondary structure (i.e. hairpin structures) into the general, well known, Invader Assay as demonstrated by Ledford since the prior art suggests such a modification to stabilize and enhance formation of target duplex formation. An artisan would have been capable of applying this known method of enhancement, i.e. favoring a target:probe formation, to a probe based assay in a predictable manner.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in that at the time of invention to utilize DNA probes constructed to be used in the invader

assay to detect RNA target since not only did the prior art recognize that DNA probes could be used in such a manner, DNA probes are more stable than their RNA counterparts. An artisan would have been capable of applying DNA probes (within the Invader Assay) to detect RNA targets in a predictable manner.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in that at the time of invention to apply the RNA detection methods of Ledford and Prudent, i.e. the Invader Assay, to microRNA, an obvious structurally equivalent species of the genus molecule RNA, since prior art suggests the detection and further study of these molecules because their abundance implies that they function in a variety of regulatory pathways.

In conclusion, given the small structure of microRNA, one of ordinary skill in the art would have been motivated to search for and apply techniques that would favor formation of target:probe formation, e.g. addition of secondary structure to probes, the use of DNA probes to detect RNA target, etc.

2. Claim(s) 33, 36, 44-47, 58, 59, 62, and 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledford et al. ("A multi-site study for detection of the factor V (Leiden) mutation from genomic DNA using a homogeneous invader microtiter plate fluorescence resonance energy transfer (FRET) assay" J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (U.S. 5,770,365), in view of Prudent et al. (U.S. 5,985,557), in view of Rather (U.S. 5,858,367), in view of Rando et al. (U.S. 5,593,835), and in view of Lau et al. ("An Abundant Class of Tiny RNAs

with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32 and 57, and in further view of Morris et al. ("Rapid reverse transcription-PCR detection of hepatitis C virus RNA in serum by using the TaqMan fluorogenic detection system J Clin Microbiol. 1996 Dec;34(12):2933-6).

The teachings of the previously applied references have been outlined in above rejections. The above references do not expressly teach a detection procedure that includes the polymerase chain reaction (PCR), more specifically, a PCR that utilizes a fluorescent probe configured for FRET detection.

Morris provides a supporting disclosure that teaches TaqMan RT-PCR encompassing the limitations set forth in the above claims (fig. 1; pg. 2934, Materials and Methods, RT-PCR, for example). Furthermore, they teach that in the TaqMan assay post amplification manipulations are reduced therefore offering significant time savings.

Thus, it would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate TaqMan PCR detection into the general, well known, Invader Assay as demonstrated by Ledford since prior art suggests such a modification to allow homogeneous detection thereby reducing experimental time. A skilled artisan would have been capable of applying this known method of enhancement, i.e. reducing experimental time, to a probe based assay in a predictable manner.

3. Claim(s) 42, 43, 66, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledford et al. ("A multi-site study for detection of the factor V (Leiden) mutation from genomic DNA using a homogeneous invader microtiter plate fluorescence resonance energy transfer (FRET) assay" J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (U.S. 5,770,365), in view of Prudent et al. (U.S. 5,985,557), in view of Rather (U.S. 5,858,367), in view of Rando et al. (U.S. 5,593,835), and in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32 and 57, and in further view of Marras et al. "Multiplex detection of single-nucleotide variations using molecular beacons" Genet Anal. 1999 Feb;14(5-6):151-6).

The teachings of the previously applied references have been outlined in above rejections. The above references do not expressly teach detection procedures that include the use of probes that form different conformations upon hybridization or the detection of polymorphisms.

Marras provides a supporting disclosure that teaches detection of single-nucleotide variants (pg. 154, col. 2, for example) through the incorporation of FRET enabled molecular beacons in a homogeneous assay (fig. 1; pg. 152, col. 2, for example). Furthermore, Marras teaches that molecular beacons are uniquely suited for the detection of single-nucleotide variants because they bind their targets with higher specificity than conventional oligonucleotide probes (pg. 152, col. 1, for example).

Thus, it would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate FRET enabled molecular beacons into the general, well known, Invader Assay as demonstrated by Ledford since prior art suggests such a modification to allow homogeneous detection. Moreover, the probes bind their targets with higher specificity than conventional oligonucleotide probes. A skilled artisan would have been capable of applying this known method of enhancement, i.e. homogeneous detection, to a probe based assay in a predictable manner.

4. Claim(s) 55, 56, 79, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledford et al. ("A multi-site study for detection of the factor V (Leiden) mutation from genomic DNA using a homogeneous invader microtiter plate fluorescence resonance energy transfer (FRET) assay" J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (U.S. 5,770,365), in view of Prudent et al. (U.S. 5,985,557), in view of Rather (U.S. 5,858,367), in view of Rando et al. (U.S. 5,593,835), and in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32 and 57, and in further view of Hyldig-Nielsin et al. (U.S. 5,985,563).

The teachings of the previously applied references have been outlined in above rejections. The above references do not expressly teach the use of peptide nucleic acids (PNAs).

Hyldig-Nielsin provides a supporting disclosure that teaches an assay using PNA probes (col. 17, lines 30-45; col. 19,20, ex. 1, for example). Hyldig-Nielsin further teaches that PNAs have a higher thermal instability of mismatching bases whereby PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes (col. 2, lines 40-55).

Thus, it would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate PNA probes into the general, well known, Invader Assay as demonstrated by Ledford since prior art suggests such a modification to provide for probes with greater specificity. A skilled artisan would have been capable of applying this known method of enhancement, i.e. probes with greater specificity, to a probe based assay in a predictable manner.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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